## REMARKS

### *i. Status of the claims*

Claims 1-6, and 8-25 are pending.

Claim 7 has been canceled.

Claims 6 and 10-24 are withdrawn.

Claim 25 has been added and is drawn to a qualification recited in original claim 1.

Claims 1-5 and 8-9 have been amended for the reasons that follow.

(a) Claims 1-5, 8, and 9 are grammatically correct

Claims 1-5, 8, and 9 have been amended for grammatical purposes, *i.e.*, to ensure the claims use proper articles, and to delete "mammalian" as suggested by Examiner Shukla.

(b) Applicants have canceled claim 7 and, therefore, the rejection under 35 U.S.C. § 112, second paragraph is moot

Purely for the sake of expediting prosecution, Applicants have canceled claim 7 without prejudice or disclaimer. Accordingly, the rejection that claim 7 is indefinite for reciting nonelected subject matter is moot.

(c) The amended claims make clear that the human chromosome fragment that is introduced into a nonhuman mammal cell is not integrated into the cell genome but exists independently

Applicants have amended the claims to qualify a cell of the nonhuman mammal as being "trans-chromosomic" and that the cell harbors a human chromosome fragment expressing at least one human cytochrome P450 gene. Support for "trans-chromosomic" can be found at Example 5 (page 77) of the application. This amendment makes clear that the human chromosome fragment harboring the P450 gene is not inserted into the genome of a transformed nonhuman mammal cell. Rather, the term "trans-chromosomic," as well as the

phrase "harbors a human chromosome fragment," specify that the chromosomal fragment resides independently from the genome of a transformed cell.

This amendment also agrees with Applicants' assertion at page 16, lines 18-22 of the specification, that microcell fusion permits introduction of a human chromosome "into a cell in an independent state without being integrated into a genome of a host, and thus such a positional effect can be avoided."

***ii. The present human chromosomal fragment is not integrated into the genome of a nonhuman mammal cell and, for this reason, the skilled person can reliably predict a consequential phenotype***

Claims 1-5, 7, and 9 have been rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Office Action at page 3. Specifically, the Examiner contends that "the limited disclosure in the specification is not deemed sufficient to reasonably convey ... that Applicants were in possession of the huge genera recited in the claims." Office Action at page 5. The Examiner believes that the working example drawn to a transformed mouse ES cell cannot be sufficiently applied to other nonhuman mammals and because "there is no description of the phenotype of any mammal other than a mouse." Office Action at page 4. The Examiner concludes that, therefore, "the phenotype(s) of the claimed animals cannot be predicted because the art of making transgenic or knockout animals is highly unpredictable." Office Action at page 4.

(a) The present application details twenty-six working examples that teach a variety of experimental techniques for making the claimed nonhuman mammal

The present application details twenty-six working examples that teach a variety of experimental techniques for making the claimed nonhuman mammal. For instance, the working examples clearly explain how to introduce a human chromosome fragment into an ES cell via microcell fusion and how to prepare a chimeric animal from such a transformed ES cell. Applicants believe that the disclosed methods are sufficiently descriptive that the skilled person could predictably transform a cell from a mammal other than the mouse and mouse cells that are exemplified in those examples.

(b) The Examiner reasons that methods that integrate DNA into a host cell genome are unpredictable. However, no DNA is integrated into the cell genome of the claimed nonhuman mammal, so the reasons for rejecting the claims do not apply

The Examiner concludes from Hammer *et al.*, *Cell*, 63, pp. 1099-1112, 1990, that "the integration of a transgene into alternative species may result in widely different phenotypic responses." This is because Hammer integrated a desired HLA-27 transgene directly into the genomes of mice and rats, but only observed a resultant disease-associated phenotype in the transgenic rats. Office Action at pages 4 and 5.

The Examiner concludes from Wood, *Comparative Medicine*, 50 (1), pp. 12-15, 2000, that the phenotype of a transgenic mouse cannot be predicted because of the nature of DNA insertion. Office Action at page 4.

Indeed, unpredictability stems from the fact that integration of an exogenous DNA molecule into a cell genome can disrupt one or more mechanisms or properties associated with that genome. Hence, Hammer reports that "the variation among transgenic rat lines most likely can be ascribed to either quantitative or qualitative differences in the expression of the transgene or to differing effects of the transgene on the host genome" (emphasis added), page 1110, line 26.

On the other hand, the trans-chromosomic fragment of the present invention is not integrated into the host cell genome and, therefore, no part of the host cell genome is directly disrupted. Hence, using microcell fusion to import a chromosome fragment into a host cell, but not into the cell genome, can be applied to species other than the exemplified mouse. The skilled artisan would understand that any phenotype exhibited by the host cell genome is due to the introduced chromosomal fragment and not due to a disruption of the native genetic material, regardless of what mammalian species has been so transformed.

Accordingly, for these reasons, Applicants assert that the claimed genera has written description support and respectfully request that this rejection be withdrawn.

***iii. The underlying basis that "major consequences" may result from integration of foreign DNA into host DNA, does not apply in the present situation because the human chromosome fragment exists in a transformed cell independently from the cell genome***

Claims 1-5 and 7-9 are rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly "does not reasonably provide enablement for any non-human mammal comprising any human cytochrome 450." Office Action at page 5. The Examiner states that there are "several significant limitations to the application of same methodology of making transgenic animals to different species." Office Action at page 6. For instance, longer gestation times, reduced litter sizes, number of fertilized eggs, and "low efficiency of gene integration" apparently exemplify such limitations. Office Action at pages 6 and 7.

The Examiner further concludes that introducing a foreign DNA into an oocyte "may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of the transgene in all the non-human mammal species will be highly variable and unpredictable." Office Action at page 8.

As explained in the preceding subsection, the foreign DNA, *i.e.*, the human chromosome fragment of claim 1, is not integrated into host chromosomal DNA. The fragment exists independently of the host genetic material. Indeed, Applicants assert that the microcell fusion method presently employed permits introduction of a human chromosome "into a cell in an independent state without being integrated into a genome of a host, and thus such a positional effect can be avoided," (page 16, lines 18-22). Therefore, the underlying basis for this rejection, *i.e.*, that "major consequences" may flow from integration of foreign DNA into host DNA, does not apply.

Applicants assert that there is no undue burden placed on the skilled artisan. To the contrary, Applicants provide the skilled person with an extensive set of working examples and experimental guidance that enable him to use microcell fusion to produce a non-mouse cell that harbors a human chromosome fragment. Since the alleged unpredictability

associated with the direct integration of foreign DNA into host DNA does not apply, Applicants assert that the microcell fusion approach is applicable across species.

Applicants append herewith, therefore, a copy of Kuroiwa *et al.*, *Nature Biotechnology*, 20, pp. 889-894, September 2002, co-authored by three of the present inventors, Yoshimi Kuroiwa, Kazuma Tomizuka, and Isao Ishida. This post-filing date publication describes the successful applicability of microcell-mediated chromosome transfer in cloning of trans-chromosomic calves that produce human immunoglobin. Accordingly, Kuroiwa *et al.* corroborates the methodology disclosed in the application and that that methodology is applicable across species.

For at least these reasons, Applicants assert that the claims 1-5 and 7-9 are enabled and respectfully request that the Examiner withdraw this rejection.

***iv. The claimed invention is not anticipated by either Li document because neither teaches a trans-chromosomic cell that comprises a P450-containing chromosome fragment that is not integrated into the cell genome***

Claims 1-5 and 7-9 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Li *et al.*, *Archives of Biochemistry and Biophysics*, 329, pp. 235-240, 1996, and by Li *et al.*, *Biochem. Biophys. Res. Comm.*, 228, pp. 312-317, 1996. Office Action at page 10.

The Li documents describe only an "M10" transgenic mouse that contains a single CYP3A7 cDNA integrated into the host cell genome downstream of the mouse metallothionein-1 promoter. Li *et al.* and Li *et al.* say nothing about a cell that harbors a human chromosomal fragment outside of the host's cellular genome. Hence, neither of the Li documents teaches a trans-chromosomic cell that comprises a P450-containing chromosome fragment as presently claimed.

For these reasons, claims 1-5 and 7-9 are not anticipated by the cited documents and Applicants therefore respectfully request that these rejections be withdrawn.

***v. Conclusion***

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 30 November 2004 By S. A. Bent

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768